

REMARKS

By this Amendment, claims 1, 3-5, 17, 37, 46-48, and 60 have been amended. Claims 29 and 30 were previously cancelled without prejudice and claims 31-36 stand withdrawn from consideration. Claims 1-28 and 37-78 are thus currently under examination in the present application. For the reasons set forth below, Applicants submit that the present amendments and arguments place this application in condition for immediate allowance.

As an initial matter, by virtue of the present amendments, claim 1 has been amended to refer to particular primer pairs that can be used to amplify HBV nucleic acids in accordance with the present invention. These specific primers were previously presented in claims 32 and 33 of the application, as filed, and can also be found throughout the specification of the present application. Accordingly, no new matter has been added by the amendments to claim 1.

In the Office Action dated April 24, 2009, the Examiner first objected to the sequence listing as failing to include nucleotide sequences which were included in Figures 2 and 3 of the present application. By the present amendments, those nucleotide sequences have now been incorporated into the revised sequence listing that is included with this response. Furthermore, by the present amendments, the specification of the present application has been amended to refer to appropriate SEQ ID NOS for those sequences in the description of the drawings. Since these sequences were previously disclosed in the drawings as filed, the Sequence Listing does not constitute new matter. As such, Applicants state pursuant to 37 C.F.R. §1.821(f) that the content of the enclosed

computer readable form and paper sequence listing are the same, and in accordance with 37 C.F.R. §1.821(g), state that the enclosed submission contains no new matter. Accordingly, Applicants further submit that the present application is in compliance with the requirements for sequence listings and thus respectfully request that the Examiner's objection be withdrawn.

In the Office Action, the Examiner also objected to Figures 1, 2, and 4 for including text that was obscured because of shading or was too small to be seen. Without addressing the merits of these objections, Applicants submit herewith clearer drawing figures which overcome any objection.

In the Office Action, the Examiner then objected to claims 9, 16, 52, and 59 for reciting SEQ ID NOS that were not elected. Applicants acknowledge that the examination conducted in conjunction with the present Office Action was performed with regard to the elected sequences, namely SEQ ID NOS: 1, 13, 15, and 17. However, Applicants have maintained the non-elected subject matter in the claims and have also included the non-elected sequences in claim 1, as amended, in order to reserve the right to request rejoinder of the non-elected sequences upon allowance of the elected sequences. Upon later determination that the non-elected sequences are not able to be rejoined, Applicants will then cancel the non-elected sequences and reserve the right to file a continuation.

In the Office Action dated April 24, 2009, the Examiner then rejected claims 3, 4, 17, 37, 46, 47, and 60 under 35 U.S.C. §112, second paragraph as being indefinite. In particular, the Examiner made several minor objections to the wording of claims 17 and

60 and also asserted that there was not antecedent basis for the term “biological sample” in claim 37. Further, the Examiner also asserted that claims 3, 4, 46, and 47 were indefinite for defining the scope of those claims in terms of a GenBank accession number. Each of these rejections has now been rendered moot by virtue of the present amendments, which are discussed in more detail below. Accordingly, Applicants respectfully traverse the Examiner’s rejections, insofar as applied to the claims as amended, and request that they be withdrawn.

With regard to the rejection of claims 17 and 60, the Examiner asserted that the phrases “well conserved among HBV” and “use is made of primers” were indefinite as it was unclear what was required to be considered “well conserved” and it was unclear what “use” was intended for the primers. By the present amendments, Applicants have removed the phrases “well conserved among HBV” and “use is made of primers” from claims 17 and 60, and have amended these claims to place the claims in proper format and to directly indicate that the two primer pairs are complementary to HBV genomic regions.

With regard to the Examiner’s rejection of claim 37 and the Examiner’s rejection of claims 3, 4, 37, 46, and 47, these rejections have also been rendered moot by virtue of the present amendments. Specifically, claim 37 has been amended to recite “a biological sample” and claims 3, 4, 46, and 47 have been amended to recite GenBank GI Number 1336554, which corresponds with GenBank AB048704 and is in accordance with the Examiner’s suggestions.

Finally, in the Office Action, the Examiner also made several rejections to the claims of the present application under 35 U.S.C. §103(a) as being unpatentable over Junker, et al. (Nucleic Acids Research. 15(24):10117-10132) and the dissertation of Garces, in combination with a variety of secondary references including: Weimer, et al. (Journal of Virology. 61(10): 3109-3113, Oct. 1987); GenBank No. AB048704; Norder, et al. (Virology. 198: 489-503, 1994); McLaughlin (U.S. 2003/0104395); Pachuk, et al. (Gene. 243: 19-25, 2000); Wilson, et al. (U.S. 6,001,557); Sells, et al. (PNAS U.S.A. 84: 1005-1009, Feb. 1987); Delaney, et al. (Antimicrobial Agents and Chemotherapy. 43(8): 2017-2026, Aug. 1999); Junker-Niepmann, et al. (EMBO Journal. 9(10): 3389-96, 1990); Yadava, et al. (Molecular Biology Today. 1(1): 17-22, 2000); Hasegawa, et al. (Journal of Virology. 68(3): 1651-1659, Mar. 1994); Jones (U.S. 2002/0072055); Halle, et al. (U.S. 6,303,308); and Liang (U.S. 5,077,192). In particular, although the Examiner acknowledges that Junker does not teach polymerase chain reaction (PCR) amplification of HBV nucleic acids using at least two primer pairs selected to obtain at least two different fragments and also acknowledges that Garces does not teach making two fragments by PCR, the Examiner has asserted that it would have been obvious to one of ordinary skill in the art to use PCR to generate greater-than-genome length HBV sequences and to place them under the control of a heterologous promoter. For the reasons set forth below, Applicants respectfully traverse these rejections and request that the rejections be withdrawn.

The claims of the present application, as amended, are directed toward methods for measuring the replication capacity of HBV and, in particular, HBV that is present in a biological sample. The claimed methods provide for PCR amplification of nucleic acids from a specific strain of HBV that is present in a biological sample, before the cloning of the fragments or the production of a corresponding pregenomic RNA (pgRNA). In this regard, it is thus noted that by using the presently-claimed methods, it is not necessary to know beforehand which strain of HBV may be present in the sample as the presently-claimed methods are versatile and can be used to assay HBV replication and test HBV susceptibility to pharmaceutical products in laboratory strains of HBV as well as in field strains of HBV, such as unidentified strains of HBV that may be present in a biological sample (e.g., a sample that is obtained from a patient that is in need of treatment for a particular strain). The primer pairs described and claimed in the present application are designed such that it is possible to recover nucleic acids from any or a vast number of HBV strains and then clone a replication-competent HBV DNA genome that corresponds to the genome of a particular strain present in a sample, including previously unknown strains of HBV, such that the susceptibility of the HBV strain to various pharmaceutical products can then be tested.

By virtue of the present amendments, the primer pairs which are used in accordance with the presently-claimed methods have now been incorporated into independent claim 1, such that claim 1 now recites a method for measuring the replication of capacity of HBV that makes use of these particular primer pairs. Applicants have unexpectedly discovered that these particular primer pairs are

sufficiently universal such that, by using the primer pairs, all of the necessary nucleic acids can be recovered from any HBV strain and the resulting HBV fragments can then be reassembled to provide a continuous DNA sequence that is capable of being transcribed into pgRNA in susceptible cells. From this pgRNA, HBV replication and the production of the particular HBV strain present in the sample can be analyzed to determine not only the replication capacity of the particular HBV strain, but also its sensitivity to a variety of pharmaceutical products, such as antiviral agents. Accordingly, by using the specific primer pairs recited in claim 1 of the present application, the methods of the present application thus allow for the recovery of both known and unknown strains of HBV by PCR amplification and the reconstruction of these fragments such that the susceptibility of an HBV strain to particular pharmaceutical products can be tested and the most appropriate treatment selected.

In contrast to the methods described and claimed in the present application, neither Junker nor Garces, either alone or in combination, teach or suggest the recovery of HBV nucleic acids from a biological sample, much less teach or suggest the recovery of HBV nucleic acids using the particular primer pairs recited in the present application, such that a linear continuous DNA sequence can be obtained and transcribed into a pgRNA that corresponds to the particular HBV strain that is present in the sample. Instead, as noted in response to previous Office Actions, Junker relates to the expression and replication of an HBV genome that is under the control of a foreign promoter. Indeed, as the Examiner acknowledges in the present Office Action, Junker does not teach or suggest PCR amplification of HBV nucleic acids using at least two primer pairs to obtain at least two

different fragments. Junker merely discloses the cloning of a known HBV genome into a plasmid in order to place the viral pgRNA under the transcriptional control of a human metallothionein II_A promoter.

Garces, on the other hand, relates to a method for constructing a greater-than-genome length HBV vector under the control of a heterologous promoter. However, as the Examiner also acknowledges in the Office Action, Garces does not teach or suggest amplifying all HBV genomic fragments to obtain a greater-than-genome length construct. Instead, Garces uses PCR amplification to produce a short HBV genomic fragment and then makes a final construct by ligation of the short HBV genomic fragment to a known linear, full-length HBV genome. In Garces, this final construct can then be inserted into a baculovirus vector and used to infect HepG2 cells and initiate synchronous HBV replication in those cells. However, similar to the cited Junker reference, the method described by Garces still only provides a method to study predetermined laboratory strains or constructs of HBV. Neither Junker nor Garces, alone or in combination, teach or suggest a method whereby particular primer pairs are used to amplify nucleic acids from a field strain of HBV, such as one present in a biological sample, and obtain at least two different amplified genomic fragments, which can then be used to produce a corresponding pgRNA.

Prior to the present invention, it was entirely unexpected that a method could be developed that allowed for the analysis of HBV replication and the testing of pharmaceutical products on field strains of HBV, particularly unidentified strains of HBV present in a biological sample. Surprisingly, however, the claimed methods, which make

use of particular, universal primer pairs to obtain at least two different amplified genomic fragments, were found to amplify all of the necessary fragments from an HBV genome such that the fragments could be recovered and assembled to produce a corresponding pgRNA in a transfected cell. Indeed, the primer pairs described and claimed in the present application enable the precise cloning of a linear, continuous HBV DNA sequence from a patient into an expression vector such that the vector precisely drives the transcription of HBV pgRNA, which is then capable of initiating intracellular HBV replication.

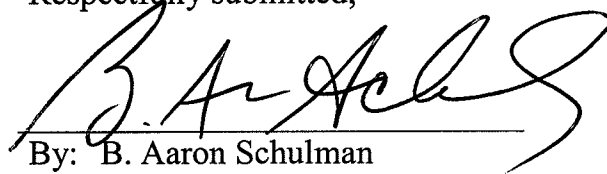
Junker and Garces do not teach or suggest this unexpected method of the present invention. These references do not teach or suggest capturing nucleic acids in a sample using universal primer pairs to obtain a continuous DNA sequence that is capable of being transcribed into a pgRNA, much less doing so with the particular primer pairs that are recited in claim 1, as amended. Moreover, neither Junker nor Garces, alone or in combination, even remotely suggest that it is possible to capture a nucleic acid of an unknown strain of HBV in a biological sample, amplify and transcribe the nucleic acid, and then test the HBV strain with a variety of pharmaceutical products. The secondary references cited by the Examiner add nothing further in this regard. These secondary references fail to teach or in any way suggest the amplification from known or unknown HBV strains from a biological sample, and do not teach or suggest the use of the particular primer pairs described and claimed in the present application such that two different HBV fragments can be obtained and used to assemble a linear continuous DNA sequence that is capable of being transcribed into pgRNA.

Accordingly, Applicants respectfully submit that the present invention is not rendered obvious by the cited references and that the claims of the present application are clearly patentable over those references. Applicants thus submit that the Examiner's rejections on the basis of those references is respectfully traversed and should be withdrawn.

In light of the amendments and arguments provided herewith, Applicants submit that the present application overcomes all prior rejections and objections, and has been placed in condition for allowance. Such action is respectfully requested.

Respectfully submitted,

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